Asymmetric Activation of Chiral Alkoxyzinc Catalysts by Chiral Nitrogen Activators for Dialkylzinc Addition to Aldehydes: Super High-Throughput Screening of Combinatorial Libraries of Chiral Ligands and Activators by HPLC-CD/UV and HPLC-OR/RIU Systems**

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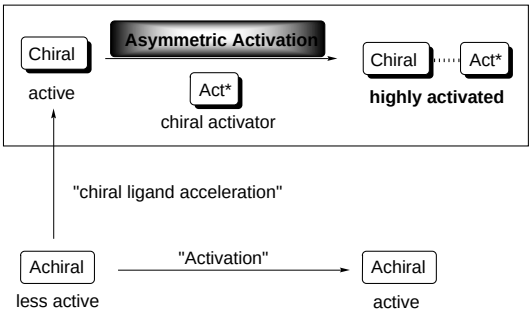
Abstract: Asymmetric catalysts, prepared by chiral ligand exchange or chiral modification, can evolve further into highly activated catalysts through engineering with chiral activators. Two new methodologies for "super high-throughput screening" (SHTS) of chiral ligands and activators have been developed as a combination of HPLC-CD/UV (CD/UV = circular dichroism/ultraviolet spectroscopy) or -OR/RIU (OR/RIU = optical rotation/refractive index unit) with a combinatorial chemistry (CC) factory. With these techniques, the % *ee* of the product is determined within minutes without separation of the enantiomeric products by using a nonchiral stationary phase. Therefore, those SHTS techniques combined with our '*asymmetric activation*' concept can provide a powerful strategy for finding the best activated chiral catalyst.

Keywords: asymmetric activation · asymmetric catalysis · binaphthol · combinatorial chemistry · zinc

Introduction

Asymmetric catalysis of organic reactions, which provide enantiomerically enriched products, is of central importance in modern synthetic and pharmaceutical chemistry.[1] Particularly, enantioselective catalysis is one of the most efficient environmentally benign processes. Therefore, the development of enantioselective catalysts is the most challenging and formidable endeavor in modern science and technology. Highly promising candidates for such enantioselective catalysts are metal complexes that bear chiral and nonracemic organic ligands. For the preparation of homogeneous asymmetric catalysts, Sharpless et al. emphasized the significance of "ligand-accelerated catalysis"[2] by construction of an asymmetric catalyst from an achiral precatalyst through ligand exchange with a chiral ligand (Scheme 1). The chiral



Scheme 1. General concept of the asymmetric activation strategy.

homo- or heterogeneous catalysts prepared by "ligand-accelerated catalysis" or "chiral modification" may evolve further into a highly activated catalyst through engineering with chiral activators (Scheme 1). The term "asymmetric activation" is proposed for this process in analogy to the activation process of an achiral reagent or catalyst to provide an activated but achiral reagent, for example, an activated zinc reagent.[3]

This asymmetric activation process is particularly useful for racemic catalysts by selective activation of one of the

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[**] OR/RIU = optical rotation/refractive index unit.

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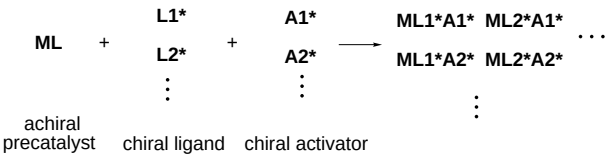
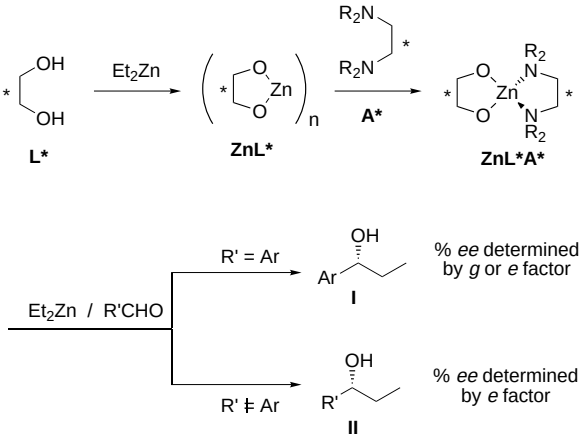
enantiomers. The advantage of this approach is that the activated catalyst can produce a greater enantiomeric excess in the products than the enantiomerically pure catalyst on its own. Thus, chiral catalysts with chiral ligands (L1*, L2*,...) may evolve further with chiral activators (A1*, A2*,...) into highly enantioselective, activated catalysts (Scheme 2).



Scheme 2. General principle for the creation of a catalyst system by asymmetric activation.

Amongst asymmetric catalysis of C–C bond-forming reactions, enantioselective addition of diorganozinc reagents to aldehydes constitutes one of the most important and fundamental asymmetric reactions.[4] Since its initial report by Oguni,[5] various chiral ligands, including α-amino alcohols, have been used for this type of reaction. However, less attention has been paid to C_2 symmetric binaphthols (BINOLs),[6] despite their wide application as chiral ligands for B,[7] Al,[8] Ti,[9] Zr,[10] and Ln[11] catalysts in enantioselective aldol, ene reactions and so forth, probably due to their lower catalytic activity and enantioselectivity for the organozinc addition reaction.[12] Recently, some modified BINOLs[13] were reported to be effective, but the parent BINOL itself is very inert to the reaction. It is reasonable to assume that the active catalytic species in the addition of diethylzinc to aldehydes is a monomeric zinc alkoxide; the cleavage of the higher aggregates may result in the activation of the catalyst system (Scheme 3).[14] The addition of a chiral nitrogen



Scheme 3. Asymmetric activation of diol–zinc catalysts by nitrogen ligands.

activator for to the BINOLs–zinc catalyst system should be one of the most efficient routes to activation, because of its strong coordinating ability to the zinc cation which facilitates the alkyl transfer. As a result, a monomeric zinc complex is expected to form in a similar manner to that of a chiral salen–zinc complex (salen = *N*,*N*′-bis(salicylidene)ethylenediamine dianion.[15] Furthermore, bimolecular combination of chiral activators with chiral diol–zinc catalysts should be more convenient than the unimolecular combination.

Combinatorial chemistry has been well recognized as a useful strategy for the discovery and optimization of drugs, metal complexes, and solid-state materials.[16] However, few studies have been reported on chiral ligand optimization for chiral metal complexes, due to the lack of high-throughput screening (HTS) methods.[17] In this regard, we report herein on a super high-throughput screening (SHTS) system. A circular dichroism (CD) detector (a JASCO CD-995 (1595) instrument) in conjunction with HPLC has been applied in the combinatorial search for enantioselective catalysts through asymmetric activation (Scheme 2) for the addition of diethylzinc to *aromatic* aldehydes, which leads to aryl-substituted carbinols of type **I** (Scheme 3).[18] This method involves the simultaneous monitoring of the CD signal ($\Delta\varepsilon$), the absorption (ε), and their ratio, called the dissymmetric or anisotropy factor ($g = \Delta\varepsilon/\varepsilon$), of a sample in HPLC on *non*chiral (*achiral*) stationary phases at a fixed wavelength in a flow system.[19] The *g* factor is independent of concentration and linearly related to the enantiomeric excess. The *g* factor was introduced by Kuhn[20] in 1930, refined by Mason[21] in 1980, and further developed by Salvadori[19b–d] and Mannschreck.[22] We have developed fast and efficient ways to determine the *ee*'s of a product library, which can be quantitatively produced by the addition of diethylzinc to *aromatic* aldehydes catalyzed by a binaphthol–zinc complex through asymmetric activation with chiral Schiff bases. With this technique, the % *ee* of the product can be determined within minutes, by using *achiral* stationary phases, without separation of the enantiomeric products. Therefore, application of HPLC-CD/UV with a combinatorial chemistry (CC) factory (Dainippon Seiki) for reactions provides a "super high-throughput screening (SHTS)" system for finding the most effective catalyst produced from asymmetric activation.[18]. We herein describe the details the SHTS of parallel solution libraries chiral ligands (L1*, L2*,...) and activators (A1*, A2*,...) for alkoxy–Zn catalysts in the addition of diethylzinc to aldehydes by using the CC factory, HPLC-CD/UV and HPLC-OR/RIU.

Experimental Section

Instrumentation (HPLC-CD/UV): The CD spectra were measured with an HPLC-CD/UV instrument with a flow cell containing optically active products. In general, a flow cell with a long 25 mm optical path length is used in order to obtain higher sensitivity. However, since the sample is in the liquid stream, multiple reflections on the wall and other effects can occur in such a long cell. These effects cause depolarization and results in reduction of sensitivity and occurrence of false peaks. Therefore, we employed a short 10 mm cell.

A CD detector can differentiate between enantiomers by measuring difference in absorbance of right and left circularly polarized light. This principle of detection gives intrinsic stability and high sensitivity. Because measurement of difference in absorption is performed within a very short period of time, 20 microseconds, dual-beam detection is in operation, whereas in optical rotation (OR) detection is from a single beam. Thus, a CD detector can generate chiral signals with higher sensitivity and stability. A JASCO CD-995 (1595) circular dichroism detector was used with an autosampler on a CrestPak C18S column (4.6 × 35 mm) with CH_3CN/H_2O (1:1) as eluent at 313 K, the flow rate being 2.5 mL min^{-1} at a pressure of

12 MPa. The HPLC system was constructed with a PU-980 pump, a DG-980-50 vacuum degasser, an AS-1559 autosampler, a CO-966 column thermostat compartment, and the JASCO CD-995 detector. The CD-995 detector allowed for the simultaneous monitoring of CD and UV absorption of compounds. In addition, CD and UV spectra could be obtained by stopped-flow scanning. For system control of HPLC, including the data processing and calculation of % *ee*, PC-based JASCO BORWIN-NT/HSS-1500 and JASCO *g*-factor calculation software on Microsoft ExcelR were used.[23] The retention time for 1-phenylpropanol was 0.6 min. Based on the dissymmetry factor (g) measured at 275 nm, the % *ee* of products could be calculated. Products and standard samples for calibration plots were analyzed automatically by the HPLC-CD system according to the sequential analysis file, which includes system control and automatic peak detection. This file has 600 sequences and saves same number of manipulated chromatograms. The peak area and retention time of CD and UV chromatograms obtained from CD detector were saved automatically in the sequential analysis file after being calculated by optimized automatic peak detection. After selecting the sequential analysis file, the peak area and retention time, for calculation of enantiomeric purity, were used with the *g*-factor calculation software on Microsoft ExcelR. On the basis of the calibration curve of based on the value of the *g* factor of standard sample, the values of the *g* factor, enantiomeric ratio, and % *ee* of the product were calculated in a few seconds.

General procedure for super high-throughput screening: All the reaction operations were performed under nitrogen. Weighed amounts of chiral ligands L* (0.01 mmol), chiral activators A* (0.01 mmol), or both (each, 0.01 mmol) were introduced into 1 mL polypropylene microtubes. By using micropipettes, CH_2Cl_2 (100 μL) and Et_2Zn (200 μL, 1M in hexane) were added. The microtubes were then set up in the CC factory,[24] the temperature was kept at 0 °C for 30 min and finally benzaldehyde (11 μL, 0.1 mmol) was introduced. After agitation for 20 h at 0 °C, the tubes were opened. The CC factory performed the programmed quench with water and separation of the organic phase.

Analysis by *g* factor: A JASCO CD-995 (1595) circular dichroism detector was used with an autosampler on a CrestPak C18S column (4.6 × 35 mm) with CH_3CN/H_2O (1:1) as eluent at 313 K, flow rate 2.5 mL min^{-1}, and pressure of 12 MPa. The HPLC system was constructed with a PU-980 pump, a DG-980–50 vacuum degasser, an AS-1559 autosampler, a CO-966 column thermostat compartment, and the JASCO CD-995 detector. The retention time for 1-phenylpropanol was 0.6 min. Based on the dissymmetry factor (g) measured for 1-phenylpropanol at 275 nm, the % *ee* of products could be calculated automatically as described above.

Analysis by *e* factor: JASCO OR-1590 and RI-1530 detectors were used with an autosampler on a CrestPak C18S column (4.6 × 35 mm) with CH_3CN/H_2O (60:40) as eluent at 313 K, flow rate 2 mL min^{-1}, and pressure of 12 MPa. The HPLC system was constructed with a PU-980 pump, a DG-980–50 vacuum degasser, an AS-1559 autosampler, a CO-966 column thermostat compartment, and the JASCO CD-995 detector. The retention time for 3-octanol was 0.6 min.

Optimized procedure: L5* (44 mg, 0.1 mmol), A9* (47 mg, 0.1 mmol), CH_2Cl_2 (1 mL) and diethylzinc (2 mL of 1M hexane solution, 2 mmol) were added under argon to a dried flask at room temperature. The flask was cooled to −78 °C, and then benzaldehyde (106 mg, 1 mmol) was introduced dropwise by a microsyringe. The reaction mixture was then stirred at −78 °C for 4 h and at −20 °C for 1 h; water (2 mL) was added to quench the reaction. The aqueous layer was extracted with diethyl ether, and the combined organic phase was washed with brine and then dried over anhydrous $MgSO_4$. The crude product was purified by column chromatography on silica gel with EtOAc/hexane (1:5) as eluent to give the pure 1-phenylpropanol as a colourless liquid in quantitative yield and 99 % *ee*. HPLC on Daicel OD-H column with eluent of hexane/2-propanol = 99:1; flow rate = 0.8 mL min^{-1}; UV detection at 254 nm; the retention time 22.9 min (*R* enantiomer), 26.0 min (*S* enantiomer).

Results and Discussion

All experiments were performed with a JASCO HPLC system. Each sample required less than 1.5 minutes for analysis. For the linearity test (Figure 1), various solutions of the samples were prepared with different enantiomeric ratios. The resulting integral areas were chosen as a measure for CD and UV values, and from these the *g* factors were calculated and summarized in Table 1. A linear correlation was observed on the *g* factors with respect to the % *ee* values with a coefficient of variation of 0.23 %.

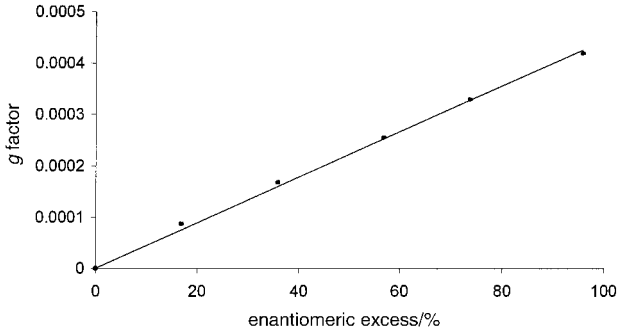


Figure 1. Linear dependency of *g* factor and % *ee* for (*S*)-1-phenylpropanol (**1**).

Table 1. Linear dependency of *g* factor and % *ee* for (*S*)-1-phenylpropanol (**1**).

ee [%] of **1**	*g* factor
0	0
17	8.63×10^{-5}
36	1.68×10^{-4}
57	2.55×10^{-4}
74	3.29×10^{-4}
96	4.19×10^{-4}

Thus, it is possible to determine the *ee* value on the basis of the *g* factor. Furthermore, *only one sample of exactly known ee-value is needed for calibration* as, by definition, the calibration curve intercepts the origin (*g* factor and % *ee* = 0).

In order to study the possible concentration dependency (Figure 2), a 10 mg mL^{-1} solution of enantio-enriched (*S*)-1-phenylpropanol (**1**, 96 % *ee*) in acetonitrile, was diluted successively and then subjected to the measurements. Table 2 lists the resulting *g* factors. Figure 2 clearly shows that the *g* factor does not depend on concentration (standard deviation = 9.57×10^{-7}). Hence, aggregation and other effects are not involved; this makes this HPLC-CD system reliable.

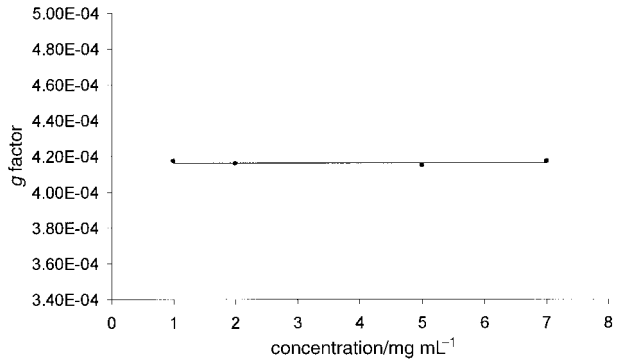


Figure 2. Linear dependency of *g* factor and concentration for (*S*)-1-phenylpropanol (**1**).

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Table 2. Linear dependency of g factor and concentration (c) for (*S*)-1-phenylpropanol (**1**).

c [mg mL^{-1}]	g factor
1	4.17×10^{-4}
2	4.16×10^{-4}
5	4.15×10^{-4}
7	4.17×10^{-4}

Therefore, a widely applicable HPLC-CD SHTS system was developed by using an *achiral* reversed-phase silica column and acetonitrile/water as the eluent. Figure 3 shows the corresponding HPLC chromatogram of (*S*)-**1** (96 % *ee*), in which the mixture is fully analyzed within 1.5 minutes (retention time of **1** is 0.6 minutes).

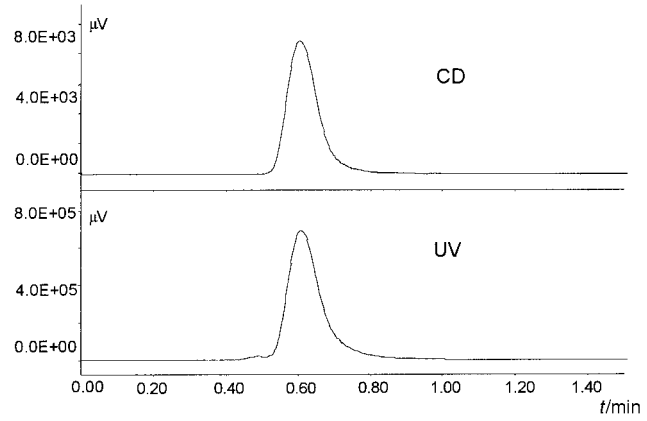
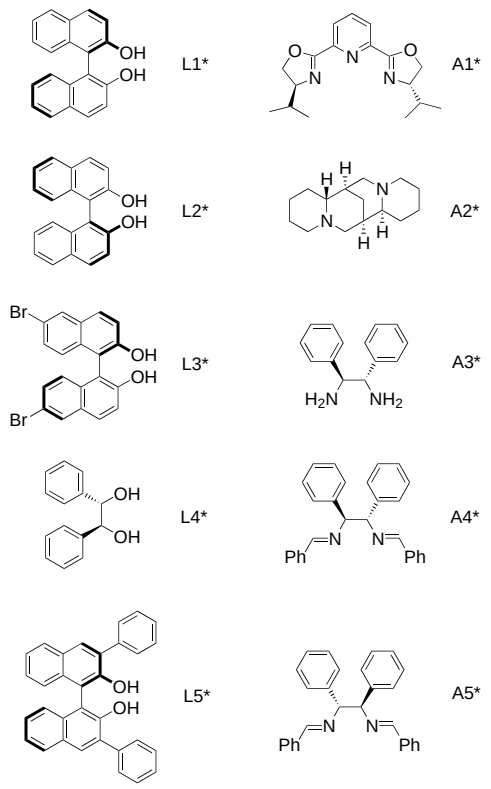


Figure 3. HPLC-Chromatogram of (*S*)-**1** (96 % *ee*).

The primary combinatory library of chiral ligands (L1*–L5*) and chiral activators (A1*–A5*) was initially examined,



from which the lead compound can be further optimized for the next generation of chiral ligands and activators. The reactions were carried out as desribed in the Experimental Section. Based on the dissymmetry (g) factor measured at 275 nm, the % *ee* of the products could be easily calculated (vide supra).

Super high-throughput screening (SHTS): As shown in Figure 4, under the experimental conditions (random screening), we observed an effect of the activation in terms of catalyst efficiency (Figure 4a, b). Enantioselectivity of the reaction was also increased by matched combination of diol ligands and nitrogen activators (Figure 4c). For example, L1* and

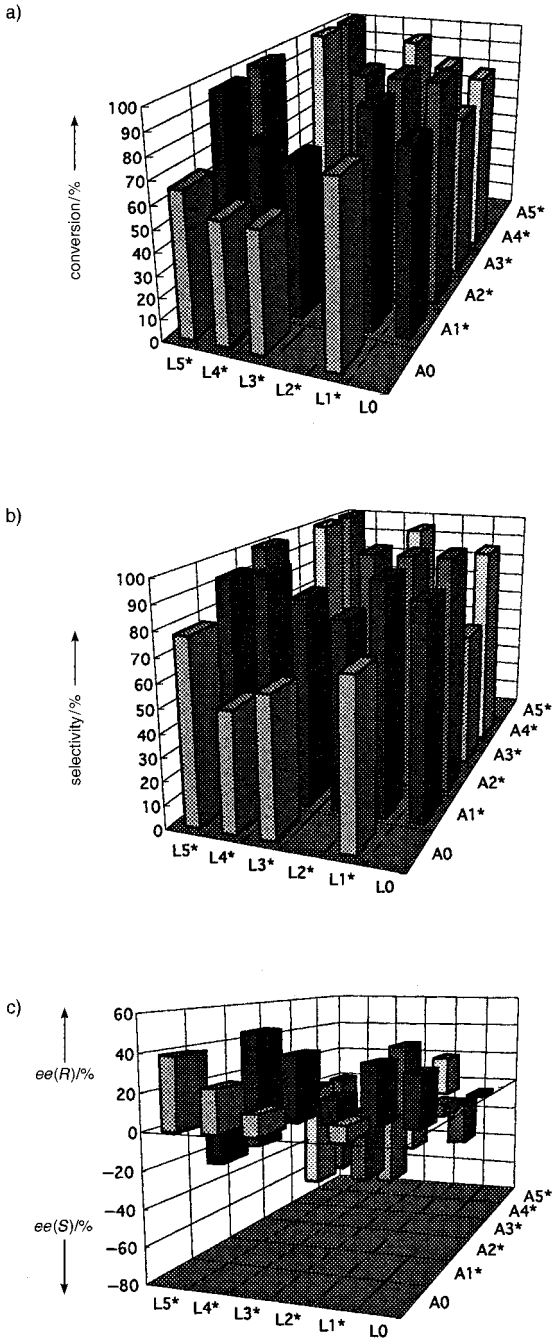


Figure 4. Random screening of chiral ligands (L0–L5*) and activators (A0–A5*). a) % conversion. b) Selectivity. c) % *ee*.

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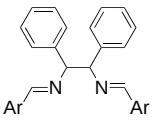
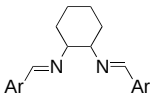
A4* promoted the reaction to give (*S*)-1-phenylpropanol in 8.2% *ee* (54% yield) and 1.1% *ee* (64% yield), respectively. However, the combined use of L1* and A4* was found to result in the product with 37.4% *ee* (*S*) and in quantitative yield. The substitution of 3- and 3′-positions with bulky phenyl groups further prevents the aggregation of BINOL/Zn and increases the enantioselectivity, because of their steric demand. The best combinations were found to be L5*/A4* and L5*/A5* to provide (*S*)-1-phenylpropanol in up to 65% *ee* and in quantitative yields.

On the basis of the results collected from primary combinatorial library, we then created the next generation library of diimines (activators; A4* to A15*) by simple

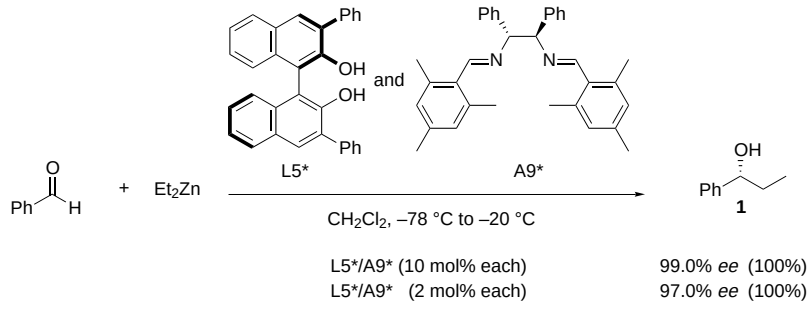




Ar		Ar	
A4*: S, S	Ph	A10*: S, S	Ph
A5*: R, R	Ph	A11*: R, R	Ph
A6*: S, S	2,6-$Cl_2C_6H_3$	A12*: S, S	2,6-$Cl_2C_6H_3$
A7*: R, R	2,6-$Cl_2C_6H_3$	A13*: R, R	2,6-$Cl_2C_6H_3$
A8*: S, S	2,4,6-$Me_3C_6H_2$	A14*: S, S	2,4,6-$Me_3C_6H_2$
A9*: R, R	2,4,6-$Me_3C_6H_2$	A15*: R, R	2,4,6-$Me_3C_6H_2$

condensation of enantiopure 1,2-diphenylethylenediamine or 1,2-diaminocyclohexane with two equivalents of aromatic aldehydes, respectively. As shown in Figure 5, all library members were found to significantly activate the Zn(L5*) complex to produce 1-phenylpropanol in higher yields and enantioselectivities than those obtained by only using the ligands themselves. Actually, the reaction could be completed within minutes in the case of L5*/A9*. The chirality of nitrogen activators had little effect on the configuration of the product, but influenced the level of enantioselectivity particularly in the cases of L5*/A8*, A9*, A12*, or A13*. Therefore, the absolute configuration of the products is determined primarily by that of diols. This observation is consistent with the empirical rule drawn by Noyori[25b] for the addition of diethylzinc to aldehydes, catalyzed by aminoalcohols. The steric hindrance of the chiral activators was found to be crucial, and hence the activator A9* provided the best results at 0 °C (100% yield, 90% *ee*).

The reaction catalyzed by the best combination L5*/A9* was further optimized by tuning the reaction temperature between −78 and −20 °C [Eq. (1)]. (*S*)-1-phenylpropanol (**1**) was thus obtained in 99% *ee* and quantitative yield (Table 3). Even when 2 mol% of L5*/A9* were used for the reaction, (*S*)-**1** was obtained in 97% *ee* and 100% yield. Under the optimized reaction conditions, the combination of L5* and A9* is proven to be extremely effective for the addition of diethylzinc to a range of aldehydes, affording the products with excellent yields and enantioselectivities (Table 3).



(1)

However, this new methodology can only be applied to UV-active compounds (such as

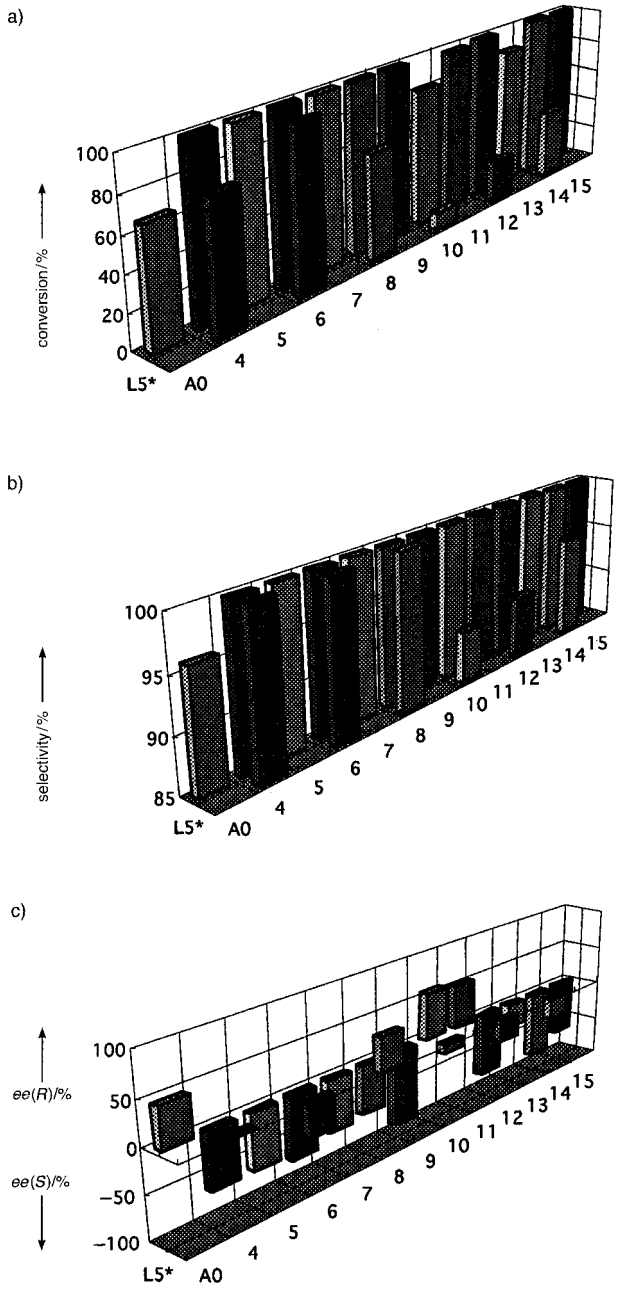


Figure 5. Screening of secondary generation library of chiral activators (A0, A4* – A15*). a) % conversion. b) Selectivity. c) % *ee*.

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Table 3. Asymmetric addition of Et_2Zn to aldehydes in the presence of L5*/A9*.

R	Yield [%] of **1**[a]	*ee* [%] of **1**[b]	Configuration[c]
phenyl	100	99.0	*S*
phenyl[d]	100	97.0	*S*
p-methoxyphenyl	100	98.5	*S*
m-methoxyphenyl[e]	100	96.4	ND[f]
p-chlorophenyl	99	98.5	*S*
p-*tert*-butylphenyl	100	99.0	ND[f]
β-naphthyl	100	93.8	*S*
α-naphthyl	93	91.5	*S*

[a] Isolated yields based on the consumed aldehydes. [b] Determined by HPLC on Daicel OD-H column unless otherwise noted. [c] Assigned by chiroptical comparison with the literature values. [d] 2 mol% of L5*/A9* were used. [e] Determined by HPLC on Chiracel OB-H column. [f] ND = not determined.

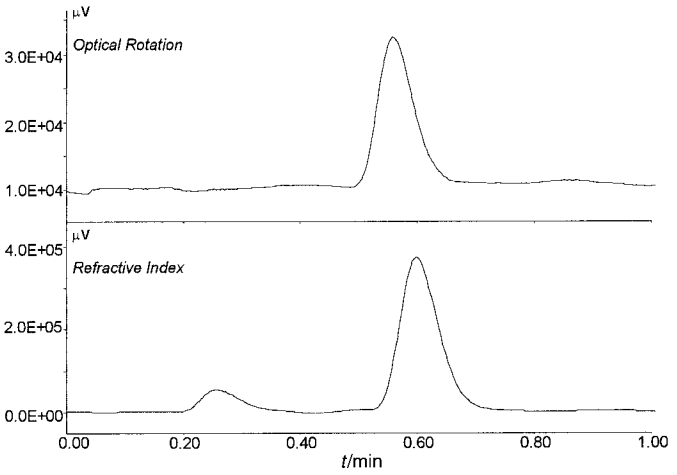

Figure 6. HPLC-Chromatogram of (*S*)-3-octanol (**2**; 80% *ee*).

type **I**). We have now developed fast and efficient ways to determine the *ee*'s of type **II** (Scheme 3) alkyl-substituted carbinols [(*S*)-3-octanol (**2**)], derived from the addition of diethylzinc to *aliphatic* rather than *aromatic* aldehydes. This was accomplished by measuring simultaneously the refractive index unit (RIU) and the optical rotation (OR) by using a JASCO RI-1530 and OR-1590 detectors, respectively,[25] of a sample in HPLC on nonchiral (*achiral*) stationary phase, in which the mixture is fully analyzed within 1.5 minutes (retention time of **2** is 0.6 minutes, Figure 6). Quantitative determination of the *ee* of product **2** was easily accomplished with a reversed-phase silica ODS column. A mixture of acetonitrile/water (60:40) was used as the eluent. A mixture of (*S*)- and (*R*)-**2**, ranging from 0 to 80% enantiomeric excess, was prepared at a concentration of 50 mg mL^{-1}.

The optical rotation normalized with respect to the refractive index unit, for which we propose the term enantiomeric (*e*) factor, is linearly related to the *ee* (Figure 7, Table 4). A linear correlation was observed on the *e* factors with respect to the % *ee* values with a coefficient of variation of 0.59%. Thus, it is possible to determine the *ee* value on the basis of the *e* factor.

More importantly, we found that dilution had almost no effect on the value of the *e* factor. A mixture of (*S*)- and (*R*)-**2** in an enantiomeric excess of 80% was prepared at a concentration of 50 mg mL^{-1}, which was then successively diluted. Figure 8 clearly shows that the *e* factor does not depend on concentration (standard deviation = 1.07863×10^{-5}; see also Table 5). Thus, aggregation and other effects are not involved, which makes this OR/RIU system reliable.

Furthermore, the *e*-factor methodology can be applied to both *aliphatic* and *aromatic* systems. For example, analysis of

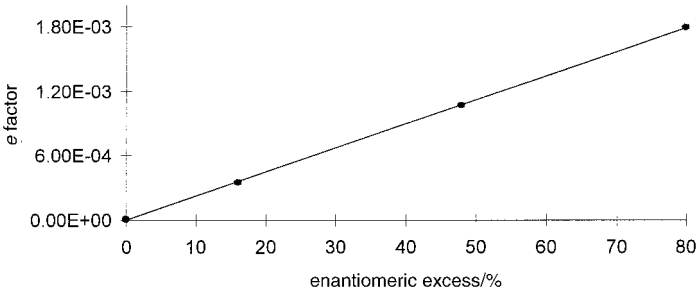

Figure 7. Linear Dependency of *e* factor and % *ee* for (*S*)-3-octanol (**2**).

Table 4. Linear dependency of *e* factor and % *ee* for (*S*)-3-octanol (**2**).

ee [%]	Optical rotation (α)	Refractive index unit (RIU)	*e* factor
80.0	21714	367078	1.79310×10^{-3}
48.0	13004	366722	1.07494×10^{-3}
16.0	4209	367056	3.47608×10^{-4}
0.1	72	367015	5.94692×10^{-6}

identical samples of **1** by the HPLC-CD/UV (*g* factor) and the HPLC-OR/RIU (*e* factor) gives virtually the same % *ee* values (Table 6).

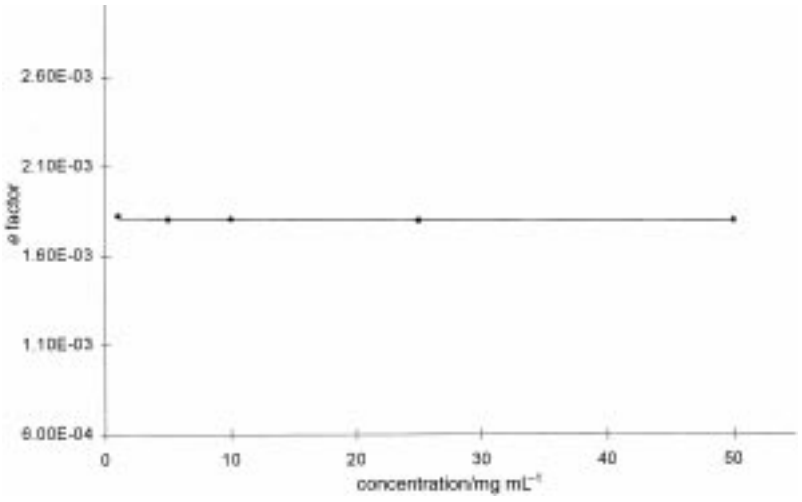

Figure 8. Linear dependency of *e* factor and concentration for (*S*)-3-octanol (**2**).

Table 5. Linear dependency of *e* factor and concentration (*c*) for (*S*)-3-octanol (**2**).

c [mg mL^{-1}]	*e* factor
50	1.82381×10^{-3}
15	1.80138×10^{-3}
10	1.80390×10^{-3}
5	1.79748×10^{-3}
1	1.79862×10^{-3}

Table 6. Determination of % *ee* of **1** by *g* and *e* factors.

ee [%] by *g* factor	*ee* [%] by *e* factor
96.0	96.0
64.6	64.1
25.4	25.6
0	0

Conclusion

In summary, we have successfully developed new strategies for super high-throughput screening[26, 27] of chiral ligands and activators by employment of the combinatorial (CC) factory and HPLC-CD/UV or -OR/RIU systems. These SHTS techniques combined with our "asymmetric activation" concept provides a powerful methodology for finding the best activated catalyst. We have demonstrated a reliable SHTS for enantiomeric excesses (*ee*s) in asymmetric catalysis through asymmetric activation.

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